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| 09/734,206 | 12/12/2000 | Trevor Douglas | 50198-154 | 1984 |

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|---|
| PARKIN, JEFFREY S |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/734,206 | DOUGLAS ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey S. Parkin, Ph.D. | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## Response to Amendment

### *Status of the Claims*

1. Acknowledgment is hereby made of receipt and entry of the amendment 09 January, 2003, wherein claims 22 and 25 were amended. Claims 21-38 are pending in the instant application.

### *35 U.S.C. § 112, First Paragraph*

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-38 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claims are directed toward virion-constrained nanoparticles comprising a non-plant virion coat protein shell surrounding a nanoparticle of non-viral origin. The disclosure provides *in vitro* methods for reassembling CCMV plant viral coat proteins into empty particles. These particles were incubated with 0.4 M $Na_2WO_4$ to produce plant virion-constrained nanoparticles. Additional methods detailing the preparation of empty CCMV plant virions followed by their incubation with $WO_4^{-2}$ ions under conditions of varying pH, to allow controlled gating, were also provided. The disclosure fails to describe the preparation of virion-constrained nanoparticles employing animal virion coat

proteins.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of nanoparticles comprising non-plant virion coat proteins. The claims encompass an exceedingly large genus of non-plant vertebrate and invertebrate viruses (e.g., *Togaviridae, Flaviviridae, Coronaviridae, Paramyxoviridae, Rhabdoviridae, Filoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Hepadnaviridae, Herpesviridae, Poxviridae, Iridoviridae*, and *Retroviridae*) and their attendant envelope proteins and glycoproteins (Murphy, 1996). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also

arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir.

1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

As noted *supra*, the disclosure fails to describe the isolation and purification of non-plant viral coat proteins. The disclosure fails to detail the preparation of virion-constrained nanoparticles comprising these virions. Finally, the specification fails to describe the loading of any given animal virion-constrained nanoparticle with various organic, inorganic, and organometallic materials. Moreover, as set forth below, the state-of-the-art vis-à-vis the preparation of virion-constrained nanoparticles is one of unpredictability. Thus, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing. Applicants are further advised that a long laundry list merely referencing other viral animal viruses does not constitute a proper written description of every species in the genus since it fails to lead the skilled artisan to any particular animal viral coat protein. *Fujikawa* v. *Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1996).

4. Claims 21-38 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for compositions containing virion-constrained nanoparticles comprising a shell of a non-plant virion coat protein or methods of their preparation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As previously set forth, the disclosure provides *in vitro* methods for reassembling CCMV, a

plant virus, viral coat proteins into empty particles. These particles were incubated with 0.4 M $Na_2WO_4$ to produce virion-constrained nanoparticles. Additional methods detailing the preparation of empty CCMV virions followed by their incubation with $WO_4^{-2}$ ions under conditions of varying pH, to allow controlled gating, were also provided. However, the claimed invention is broadly directed toward non-plant virion coat proteins that are employed in the preparation of virion-constrained nanoparticles.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the identification, isolation, and purification of suitable non-plant viral proteins that can reasonably be expected to function in the desired manner. The claims encompass an exceedingly large genus of non-plant viruses (e.g., *Togaviridae*, *Flaviviridae*, *Coronaviridae*, *Paramyxoviridae*, *Rhabdoviridae*, *Filoviridae*, *Orthomyxoviridae*, *Bunyaviridae*, *Arenaviridae*, *Hepadnaviridae*, *Herpesviridae*, *Poxviridae*, *Iridoviridae*, and *Retroviridae*) and their attendant envelope proteins and glycoproteins (Murphy, 1996). However, the disclosure fails to describe the isolation, purification, and preparation of virion-constrained nanoparticles comprising any of the

aforementioned non-plant viral coat proteins. Moreover, it is art-recognized that the mechanisms of viral assembly are complex and poorly understood (Dong *et al.*, 1993). Proper virion assembly often requires an orchestrated interaction between both viral and cellular proteins. As Dong *et al.* (1993) reported, "The nature of protein-protein interactions during retrovirus assembly is not well understood, and molecular genetic analyses of functional regions within the gag and env gene products are only beginning to provide information in this regard." The specification does not describe the preparation of virion-constrained nanoparticles from any other virus, excluding CCMV. However, the broadly recited claim language applies to a multitude of viral coat proteins, many whose role in virion assembly remains to be elucidated, obtained from any prokaryotic, eukaryotic, plant, protozoan, or virus-like particles. However, applicants have not set forth sufficient guidance in the specification pertaining to the identification or selection suitable viral coat proteins, purification protocols, reassembly protocols, gating conditions, and delivery procedures.

2) The disclosure fails to provide a single working embodiment involving a non-plant virion coat protein. The disclosure fails to describe the preparation of a virion-constrained nanoparticle comprising a non-plant virion coat protein and the subsequent loading and unloading of said nanoparticle. As discussed in this rejection, the state-of-the-art is one of unpredictability. Considering this unpredictability and the lack of guidance provided in the disclosure, several working embodiments employing non-plant viral coat proteins obtained from diverse sources would be required to enable the breadth of the claimed invention.

3) The claims are of excessive breadth and encompass a large genus of genotypically and phenotypically diverse non-plant viruses. The vast majority of the "coat proteins" encompassed by the claim language bear little or no genetic relatedness. The claims encompass an

exceedingly large genus of non-plant viruses including vertebrate and invertebrate viruses (e.g., *Togaviridae, Flaviviridae, Coronaviridae, Paramyxoviridae, Rhabdoviridae, Filoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Hepadnaviridae, Herpesviridae, Poxviridae, Iridoviridae,* and *Retroviridae*) and their attendant envelope proteins and glycoproteins (Murphy, 1996). The lack of working embodiments fails to support the breadth of the claimed invention. Moreover, applicants are reminded that the first paragraph of 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification (refer to M.P.E.P. §§ 706.03(n) and 796.03(z)). *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (CAFC 1991). Particularly where the subject matter is directed towards arts where the results are unpredictable. *In re Sol*, 1938 CD 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield* 1940 CD 351; 518 O.G 255. Clearly, the specification fails to provide sufficient guidance to enable the breadth of the claimed invention.

4) The state-of-the-art vis-à-vis the preparation of non-plant virion-constrained nanoparticles is one of unpredictability. As previously set forth, the field of molecular nanotechnology is in it's infancy, and not surprisingly, there are a number of limitations concerning it's application. Kaehler (1994) reviews the state-of-the-art and concludes that while there are many potential applications for nanotechnology, these applications have yet to be realized. The author states (refer to first paragraph, page 1799) that "Today we are in the frustrating position of being able to design many things that we believe will work without being able to build any of them." The author further discusses the future role that self-assembling proteins may play in nanotechnology.

Additional teachings from Douglas *et al.* (1987) review some of the caveats associated with developing effective nanoparticles for drug delivery. The authors conclude that several physicochemical characteristics influence the ability of nanoparticles to be targeted effectively to the target site. It was reported (refer to third paragraph, page 234) that "Particle size, shape, and number, together with surface charge and surface characteristics, all influence the biofate of colloids upon injection." Additional concerns arise from limitations associated with drug loading, drug release, nanoparticle toxicity, and the immunogenicity of the nanoparticle under study (refer to pages 245-251). Finally, the authors emphasize (refer to penultimate paragraph, page 255) that "Site-specific drug delivery using colloidal carriers is a highly complex area. Before further progress can be made, a greater understanding of the basic physiological and biochemical parameters will be required."

Douglas (1996) also provides any overview of the biomimetic synthesis of nanoscale particles in organized protein cages. A number of limitations have precluded the advancement of this field as set forth by the authors (refer to first paragraph, page 92) who stated that "There remain difficulties to overcome such as instability to particle aggregation, inhomogeneous particle size distributions, insolubility of host matrices, and an inability to extract the material from the host matrix." It was further reported that the only system that routinely provided reproducible results involved ferritin nanoparticles. However, the authors cautioned that only ferritin from a single source (e.g., equine spleen) had been routinely examined. Ferritins obtained from different sources may display different and unacceptable solution chemistry properties thereby obviating their use as nanoparticles. Moreover, the process of nanoparticle assembly involves several complicated steps including oxidation, hydrolysis, nucleation, aggregation, and particle loading.

Finally, Houk *et al.* (1996) provide several concerns regarding

gating as a control element for nanoparticle loading. The authors report that some host molecules have small portals that preclude guest or solvent passage through the molecule into the interior of the particle, other hosts have large portals that are not readily influenced and fail to form any stable complex with the guest molecule, and finally, some host molecules have small portals that admit guest molecules only under specific solvent conditions.

The instant application fails to provide adequate guidance pertaining to the identification, isolation, and purification of suitable non-plant virion coat proteins that will function in the desired manner. The disclosure only provides a single working embodiment, one that does not even include a non-plant virion coat protein. Moreover, the prior art clearly provides a number of rational scientific caveats (e.g., nanoparticle instability due to particle aggregation; inhomogeneous particle size distributions; insolubility of host matrices; inability to extract the material from the host matrix; and inability to control gating mechanisms) that would preclude the skilled artisan from practicing the claimed invention. Applicants fail to provide any guidance pertaining to any of these critical parameters. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

***Response to Arguments***

5. Applicants traverse and submit that the invention is actually based upon a simple premise involving the ability of virion coat proteins to assemble into a shell that can easily be loaded with desirable substances. Contrary to applicants' assertion, as the prior art indicated, this process is not nearly as simple as asserted. There are a number of factors that can complicate the preparation of non-plant virion-constrained nanoparticles including,

*inter alia*, the physicochemical properties of the coat protein (which influence particle size, shape, number, and surface charge), drug loading, drug release, nanoparticle toxicity, and nanoparticle immunogenicity. Applicants' response fails to provide any objective data that addresses each of these concerns. Applicants further argue that the Examiner has failed to adduce any evidence demonstrating that the claimed invention would not work. Applicants are directed toward the preceding rejection and the art relied upon therein. Several parameters were addressed that would clearly lead the skilled artisan to that the invention could not be practiced without undue experimentation. These are not mere observations by the Examiner, but rather concerns raised in the prior art. Applicants' response fails to provide any evidence that directly addresses these concerns.

Applicants provided copies of a number of publications directed toward nanotechnologies in support of their position (see Appendix C). All of the publications relied upon were post-filing date submissions. Applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the effective filing date of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). Accordingly, these submissions are insufficient to establish the state-of-the-art at the time of filing.

Applicants provided copies of several declarations from Drs. Zlotnick, Smith, Johnson, Young, and Douglas, all attesting that the claimed invention is clearly enabled. These declarations are non-persuasive for the reasons of record set forth *supra*. These documents fail to provide any data addressing the various caveats

raised in the rejection. Applicants are reminded that declaratory arguments must be factually supported by appropriate evidence. *In re De Blauwe*, 736 F.2d 699, 705, 222 U.S.P.Q. 191, 196 (Fed. Cir. 1984). *In re Lindner*, 457 F.2d 506, 508, 173 U.S.P.Q. 356, 358 (C.C.P.A. 1972). *Ex parte George*, 21 U.S.P.Q.2d 1058 (Bd. Pat. App. & Inter. 1991). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. App. & Inter. 1989). *In re Beattie*, 974 F.2d 1309, 24 U.S.P.Q.2d 1040 (Fed. Cir. 1992). *Ex parte George*, 21 U.S.P.Q.2d 1058 (Bd. Pat. App. & Inter. 1991). *In re Brandstadter*, 484 F.2d 1395, 179 U.S.P.Q. 286 (C.C.P.A. 1973). The only evidence was provided by Dr. Young who demonstrated that a paratungstate mineral could be encapsulated within a norwalk virion-constrained nanoparticle. However, this declaration failed to provide a use for said nanoparticle. Thus, it is not readily manifest if this example constitutes a full working embodiment.

***Correspondence***

6. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 O.G. 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242, (703) 305-3014, or (703) 308-4315. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

7. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 9:00 AM to 7:00 PM (Eastern Standard Time). A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner are unsuccessful, the Examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (703) 308-1122 or (703) 308-4027,

respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist at (703) 308-1235.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Technology Center 1600

20 April, 2003